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Crossed aldol reaction using cross-linked polymer-bound lithium dialkylamide

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Abstract—Cross-linked polymer-bound lithium dialkylamides were employed in crossed aldol reaction of various carbonyl compounds with aldehydes to afford the corresponding β-hydroxycarbonyl compounds. The introduction of spacer chains to the polymer-bound lithium dialkylamide between the base moiety and the polystyrene backbone effectively enhanced yields of the desired aldol adducts. Sometimes better yields were obtained by using the polymer-bound reagent having an appropriate spacer-chain with those obtained using lithium diisopropylamide under homogeneous conditions. Repeated use of these polymeric reagents was demonstrated with no loss of efficiency.

1. Introduction

Sterically hindered non-nucleophilic strong bases are useful reagents in preparing carbanions, which undergo various reactions with a variety of electrophiles to afford the corresponding products. Although diisopropylaminomagnesium bromide was first introduced as a sterically hindered non-nucleophilic metal amide in organic synthesis,[1] lithium dialkylamides represented by lithium diisopropylamide (LDA) are widely employed as a hindered non-nucleophilic strong base for the generation of various carbanions by deprotonation of weakly acidic protons in the presence of a variety of functional groups.[2] For example, the lithium dialkylamides form regio- and geometrically controlled enolates from carbonyl compounds,[3,4] which facilitate regio- and stereoselective crossed aldol reactions.[4] Recently, asymmetric synthesis using chiral lithium dialkylamides has been studied extensively.[5–15]

Much attention has been directed to polymer-bound reagents in recent years, because they are easily removed from the reaction medium and can be reused many times easily in comparison with their non-immobilized reagents.[16–24] However, only a few have been reported on the preparation and utilization of polymer-bound metal dialkylamide in organic synthesis in spite of the importance of metal dialkylamides.[25–31] The first attempt to use cross-linked polystyrene-supported lithium dialkylamide as a stronger base than polymer-bound trityllithium for the deprotonation of 1,1-diphenyl-2-chloroethylene was reported in 1981.[25]

Immobilization of chiral metal dialkylamide and its use in enantioselective deprotonation reactions of ketones have emerged.[26,27] In 1999 Majewski et al. prepared soluble and insoluble polymer-supported chiral lithium dialkylamides, then examined the asymmetric crossed aldol reaction of some cyclic ketones to benzaldehyde and enantioselective deprotonation reactions of tropinone, followed by an acylation with trichloroethyl chloroformate.[26] They showed that good enantioselectivity was obtained using the soluble polymer in the presence of lithium chloride. Polymer-supported chiral magnesium dialkylamides were also prepared and were shown to be effective in the deprotonation of 4-substituted and 2,6-disubstituted cyclohexanones, affording the corresponding optically active enol silyl ethers.[27] A stoichiometric amount of polymer-supported chiral lithium dialkylamide has also been employed in the reaction of cyclohexene oxide.[28] During the course of our investigation on the enantioselective isomerization of *meso*-epoxides into highly optically active allylalcohol derivatives, we have already reported the preparation and the use of polymer-bound achiral lithium *N*-alkyl-4-vinylbenzylamide in a catalytic system as an effective regenerator of chiral bases.[29,30]

Although polymer-supported metal dialkylamides were employed in the generation of chiral enolates from cyclic ketones as mentioned above,[26,27] generation of metal enolates by polymer-supported simple achiral metal amides and utilization of the enolate in aldol reaction have not been

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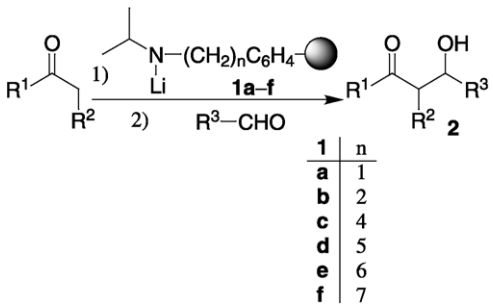
investigated systematically. In this article we report in detail on the preparation of polymer-bound lithium dialkylamides **1a–f** and their use in crossed aldol reactions between various carbonyl compounds such as ketones, esters, and amides, and aldehydes since aldol reaction is one of the most fundamental and important reactions (Scheme 1).[31]



1	n
a	1
b	2
c	4
d	5
e	6
f	7

Scheme 1.

2. Results and discussion

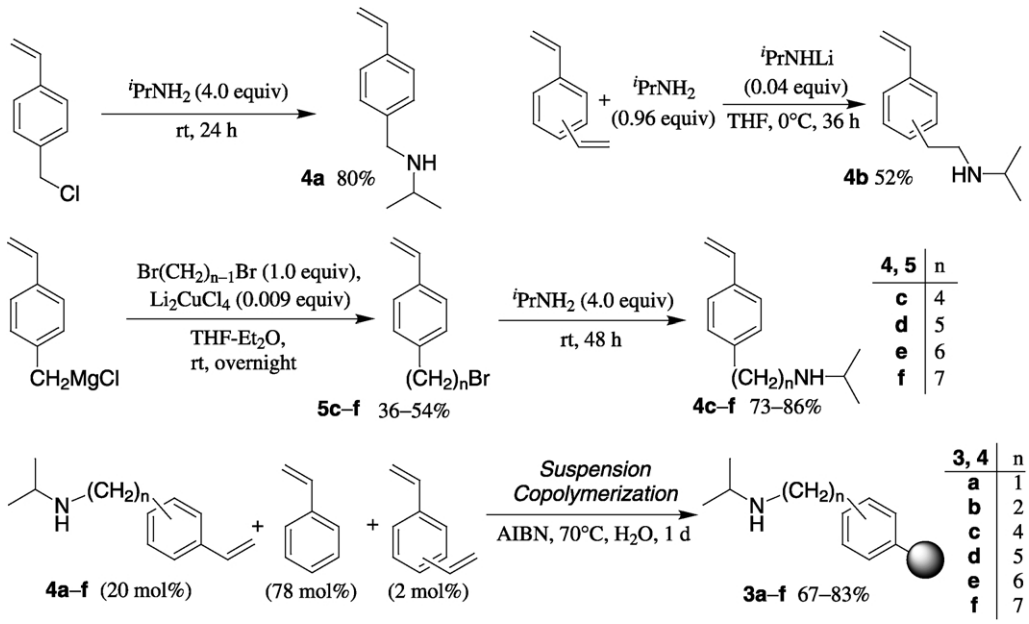
2.1. Synthesis of precursors of lithium dialkylamides

N-Isopropyl-4-vinylbenzylamine (**4a**) (n=1) was easily obtained by the alkylation of isopropylamine (4.0 equiv.) by 4-vinylbenzyl chloride (1.0 equiv.) at rt for 24 h in 80% yield. *N*-Isopropyl-2-(vinylphenyl)ethylamine (**4b**) (n=2) was prepared from isopropylamine (0.96 equiv.) and divinylbenzene (1.0 equiv.) in the presence of a catalytic amount of lithium isopropylamide (0.04 equiv.) according to a procedure similar to that reported by Tsuruta et al.[32] *N*-Isopropyl-ω-(4-vinylphenyl)alkylamines (**4c–f**) (n≥4) were obtained in good yields (73–86%) by the reaction of isopropylamine (4.0 equiv.) and bromoalkylstyrenes **5c–f** (1.0 equiv.) at rt for 48 h. The ω-bromoalkylstyrenes **5c–f** were obtained in reasonable yields (36–54%) by the cross-coupling reaction[33] of α,ω-dibromoalkanes (1.0 equiv.) with 4-vinylbenzylmagnesium chloride (1.0 equiv.) in the presence of lithium tetrachlorocuprate (0.009 equiv.) at rt overnight.

Each of the resulting monomer **4a–f** (20 mol%) was copolymerized with styrene (78 mol%) and divinylbenzene (2 mol%) in the presence of 2,2′-azobisisobutyronitrile (AIBN) according to the method similar to that described previously,[30] and the corresponding polymer-bound dialkylamines **3a–f** were obtained. The procedures are summarized in Scheme 2.

2.2. Crossed aldol reaction between 3-pentanone and benzaldehyde using polymer-bound lithium *N*-isopropyl-4-vinylbenzylamide

In the first place, the aldol reaction of 3-pentanone with benzaldehyde was examined by using 1.2 equiv. of polymer-bound lithium *N*-isopropyl-4-vinylbenzylamide **1a** as a base. Namely, to a suspension of polymer-bound *N*-isopropyl-4-vinylbenzylamine **3a** (amine content: 1.68 mmol/g; particle size: 50–100 mesh; cross-linked with 2 mol% of divinylbenzene, 750 mg, 1.3 mmol) in THF (6 mL) was added a hexane solution of butyllithium (1.54 M, 0.78 mL, 1.2 mmol) dropwise at rt and the reaction mixture was stirred for 0.5 h. A THF (2 mL) solution of 3-pentanone (86.1 mg, 1.0 mmol) was added to the reaction mixture at −78 °C and stirring was continued at the temperature for 15 min. After an addition of THF (2 mL) solution of benzaldehyde (127 mg, 1.2 mmol), the reaction mixture was stirred at −78 °C for 90 min. 1-Hydroxy-2-methyl-1-phenyl-3-pentanone (**2a**) was obtained in 65% yield after the work up of the reaction (Conditions A, Table 1, entry 1). As insufficient formation of the lithium enolate of 3-pentanone was assumed to be the reason for the rather low yield, the reaction temperature was gradually increased to rt during the 15 min in order to complete the generation of the enolate after stirring the mixture at −78 °C for 15 min. The yield of aldol **2a** was increased to 71% (Conditions B, Table 1, entry 2). Although still lower than

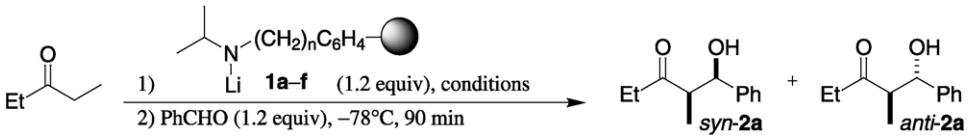


4, 5	n
c	4
d	5
e	6
f	7

3, 4	n
a	1
b	2
c	4
d	5
e	6
f	7

Scheme 2.

Table 1. Aldol reaction of 3-pentanone with benzaldehyde using polymer-bound lithium dialkylamides **1a–f**



Entry	Li-amide	*n*	Conditions[a]	Yield (%)[b]	*syn*:*anti*[c]
1	**1a**	1	A	65	68:32
2	**1a**	1	B	71	69:31
3	**1b**	2	A	65	69:31
4	**1b**	2	B	78	71:29
5	**1c**	4	A	80	68:32
6	**1c**	4	B	87	71:29
7	**1d**	5	A	82	69:31
8	**1d**	5	B	90	69:31
9	**1e**	6	A	80	69:31
10	**1e**	6	B	89	72:28
11	**1f**	7	A	77	68:32
12	**1f**	7	B	87	71:29
13	LDA	—	A	88	62:38
14	LDA	—	B	91	62:38

[a] Conditions A: the enolate was generated at −78 °C for 15 min. Conditions B: the enolate was generated at −78 °C for 15 min and then the resulting mixture was allowed to warm to rt for 15 min.
[b] Isolated yield of aldol **2a**.
[c] Determined by ^{1}H NMR analysis.

those obtained using LDA (Table 1, entries 13 and 14), slightly higher *syn*/*anti* ratios were obtained in the reaction using polymer **1a** (Table 1, entries 1 and 2).

2.3. Effect of spacer-modified polymer-bound lithium dialkylamides on the aldol reaction between 3-pentanone and benzaldehyde

Next, we examined polymer-bound lithium dialkylamide with several spacers between the base site and the polymer support so as to improve the yield of the aldol reaction, since the modification of polymer-bound reagents with spacers sometimes enhance their performance.[34,35] The aldol reaction between 3-pentanone and benzaldehyde was examined using polymer-bound lithium dialkylamide **1b–f** under Conditions A and B as described in Section 2.2. Although the same yield (65%) was observed using polymer **1a** or **1b** under Conditions A (Table 1, entries 1 and 3), the yield was improved to 78% using polymer **1b** under Conditions B (Table 1, entry 4). Then spacer-modified polymer-bound lithium dialkylamide **1c–f** was employed in the reaction under Conditions A as well as Conditions B. As the chain length was elongated up to a pentylene group, the yield of aldol **2a** was gradually improved to 90% under Conditions B (Table 1, entry 8), although longer spacers ($n>5$) had very little influence on the yield (Table 1, entries 10 and 12). Thus, almost the same yield as LDA (Table 1, entries 13 and 14) was realized using **1d** under Conditions B. The *syn*/*anti* ratio of the product **2a** was higher in every case than that observed when LDA was used.

2.4. Aldol reaction of 3-pentanone and cyclohexanone with aldehydes using spacer-modified polymer-bound lithium dialkylamide

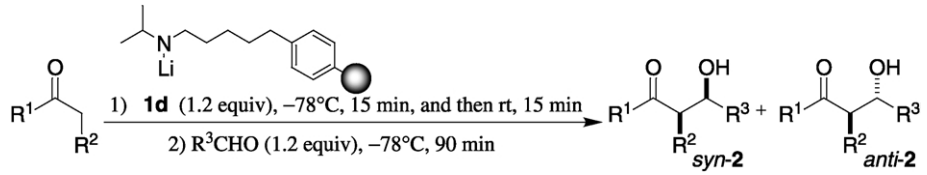
As good results were obtained in the reaction of 3-pentanone and benzaldehyde using **1d**, the reaction of 3-pentanone and cyclohexanone with several aldehydes using **1d** was examined under Conditions B employing a procedure similar to that described in Section 2.2. The results are summarized in Table 2 along with the results obtained using LDA in place of **1d**. In most cases the yields were comparable to those obtained using LDA and slightly higher selectivities were observed in some cases (Table 2, entries 1, 3, 4, 7, and 9) when the spacer-modified polymer-bound reagent **1d** was used.

2.5. Aldol reaction of methyl ketones with several aldehydes using spacer-modified polymer-bound lithium dialkylamide

Next, the aldol reaction of several methyl ketones with aldehydes was investigated in order to examine the regioselectivity of the reaction. The results are summarized in Table 3. At first, the aldol reaction between 2-pentanone and benzaldehyde was carried out using polymer-bound lithium dialkylamide **1a** under Conditions B. The aldol adduct, 1-hydroxy-1-phenyl-3-hexanone (**2k**), was obtained regioselectively in 67% yield (Table 3, entry 1). In contrast to the cases of the reaction of 3-pentanone shown in Table 1, Conditions A gave a better yield (76% yield, Table 3, entry 2). By using spacer-modified polymer-bound lithium dialkylamide **1d** under Conditions A, the yield of aldol **2k** was further increased to 88% (Table 3, entry 3). Then, under Conditions A, the aldol reaction of 2-pentanone with 3-phenylpropanal, cyclohexanecarbaldehyde, or 2-methylpropanal was examined using **1a** as well as **1d**. Corresponding aldol adducts **2l–n** were obtained in good to high yields using **1d**. Better yields as compared to those by using LDA were obtained for all aldehydes examined using **1d** (Table 3, entries 3, 5, 7, and 9).

Enolate was also regioselectively generated from 4-methyl-3-penten-2-one with polymer **1a** and **1d**, and 1-hydroxy-5-

Table 2. Aldol reaction of 3-pentanone and cyclohexanone with aldehydes using spacer-modified polymer **1d**



Entry	Aldol adduct	R^1	R^2	R^3	Yield (%)[a,b]	*syn*:*anti*[b,c]
1	**2a**	Et	Me	Ph	90 (91)	73:27 (62:38)
2	**2b**	Et	Me	*p*-ClC_6H_4	88 (89)	74:26 (77:23)
3	**2c**	Et	Me	*o*-$MeOC_6H_4$	84 (83)	65:35 (53:47)
4	**2d**	Et	Me	*trans*-PhCH=CH	93 (83)	66:34 (60:40)
5	**2e**	Et	Me	*c*-C_6H_{11}	82 (78)	40:60 (29:71)
6	**2f**	Et	Me	$Ph(CH_2)_2$	88 (90)	70:30 (71:29)
7	**2g**	Et	Me	*n*-Pr	65 (70)	72:28 (70:30)
8	**2h**	$-(CH_2)_4-$		Ph	82 (73)	27:73 (25:75)
9	**2i**	$-(CH_2)_4-$		*i*-Pr	59 (61)	3:97 (4:96)
10	**2j**	$-(CH_2)_4-$		$Ph(CH_2)_2$	56 (64)	30:70 (29:71)

[a] Isolated yield of aldol **2a**–**j**.
[b] The figures in parentheses are the results obtained by using LDA in place of polymer-bound lithium dialkylamide **1d**.
[c] Determined by ^1H NMR analysis.

methyl-1-phenyl-4-hexen-3-one (**2o**) was obtained in 81% yield in both cases (Table 3, entries 10–12). A side reaction, e.g. 1,4-addition of polymer **1a** and **1d** to the carbon–carbon bond of 4-methyl-3-penten-2-one, was not problematic (Table 3, entry 11).

Then the reaction of acetone, the least hindered ketone, with benzaldehyde was examined using polymer-bound lithium dialkylamide **1a** and **1d**. The aldol, 4-hydroxy-4-phenyl-2-butanone (**2p**), was obtained only in a moderate yield (60%) when **1a** was used. The yield was improved to 80% using **1d**.

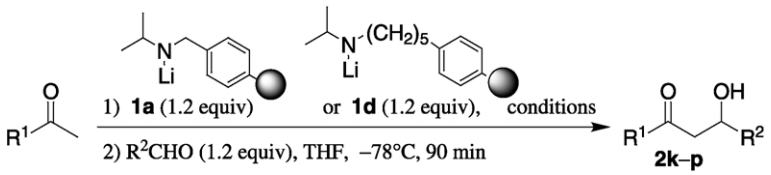
As described above, polymer-bound lithium dialkylamide effectively generates the enolate regioselectively from methyl ketones, and the corresponding aldol products were obtained in good yields by the subsequent reaction with aldehydes.

2.6. Aldol reaction of propionic acid esters with aldehydes using polymer-bound lithium dialkylamides

As polymer-bound lithium dialkylamides **1a** and **1d** were successfully employed to generate enolates from ketones and to afford the corresponding aldols in the reaction with aldehydes, we next examined the generation of enolates from propionic acid esters and their reaction with aldehydes.

Enolate of 2,6-dimethylphenyl propionate (DMP propionate) was generated using **1a** at −78 °C for 15 min

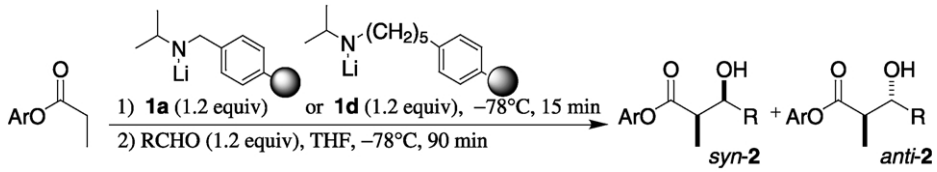
Table 3. Aldol reaction of methyl ketones with several aldehydes using polymer-bound lithium dialkylamides



Entry	Aldol adduct	R^1	R^2	Li-amide	Conditions[a]	Yield (%)[b]
1	**2k**	*n*-Pr	Ph	**1a**	B	67
2	**2k**	*n*-Pr	Ph	**1a**	A	76
3	**2k**	*n*-Pr	Ph	**1d**	A	88 (83)[c]
4	**2l**	*n*-Pr	$Ph(CH_2)_2$	**1a**	A	57
5	**2l**	*n*-Pr	$Ph(CH_2)_2$	**1d**	A	93 (86)[c]
6	**2m**	*n*-Pr	*c*-C_6H_{11}	**1a**	A	63
7	**2m**	*n*-Pr	*c*-C_6H_{11}	**1d**	A	82 (79)[c]
8	**2n**	*n*-Pr	*i*-Pr	**1a**	A	60
9	**2n**	*n*-Pr	*i*-Pr	**1d**	A	79 (73)[c]
10	**2o**	Me_2C=CH	Ph	**1a**	B	81
11	**2o**	Me_2C=CH	Ph	**1d**	B	81 (84)[c]
12	**2o**	Me_2C=CH	Ph	**1d**	A	81
13	**2p**	Me	Ph	**1a**	A	60
14	**2p**	Me	Ph	**1d**	A	80 (85)[c]

[a] Conditions A: the enolate was generated at −78 °C for 15 min. Conditions B: the enolate was generated at −78 °C for 15 min and then the resulting mixture was allowed to warm to rt for 15 min.
[b] Isolated yield of aldol **2k**–**p**.
[c] The figures in parentheses are the results obtained by using LDA in place of polymer-bound lithium amide **1a** and **1d**.

Table 4. Aldol reaction of propionic acid aryl esters with aldehydes using polymer-bound lithium dialkylamides



Entry	Ar[a]	R	Adduct	Base	Yield (%)[b]	*syn*:*anti*[c]
1	DMP	Ph	**2q**	**1a**	32[d]	17:83
2	DMP	Ph	**2q**	**1d**	72 (85)[e]	23:77 (11:89)[e]
3	BHT	Ph	**2r**	**1a**	25[f]	7:93
4	BHT	Ph	**2r**	**1d**	92 (97)[e]	3:97 (<2:98)[e]
5	BHT	*c*-C_6H_{11}	**2s**	**1d**	64	<2:98
6	BHT	*i*-Pr	**2t**	**1d**	79	<2:98
7	BHT	*n*-Pr	**2u**	**1d**	82	3:97

[a] DMP=2,6-dimethylphenyl. BHT=2,6-di-*tert*-butyl-4-methylphenyl.
[b] Isolated yield of aldol **2q**–**u**.
[c] Determined by ^{1}H NMR analysis.
[d] The 2,6-dimethylphenyl propionate was recovered in 68%.
[e] The figures in parentheses are the results obtained by using LDA in place of polymer-bound lithium amides **1a** and **1d**.
[f] The 2,6-di-*tert*-butyl-4-methylphenyl propionate was recovered in 70%.

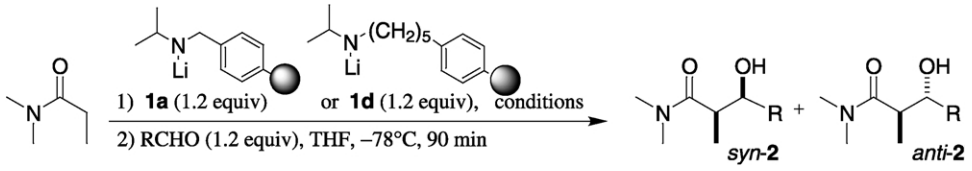
(Conditions A) and the reaction of the enolate with benzaldehyde was carried out at −78 °C for 90 min (Table 4, entry 1). 3-Hydroxy-2-methyl-3-phenylpropionic acid 2,6-dimethylphenyl ester (**2q**) was obtained in only 32% yield (*syn*/*anti*=17:83) with the recovery of the starting material (68%). Then, the reaction temperature was gradually increased to rt during the 15 min after stirring the mixture at −78 °C for 15 min (Conditions B). However, the yield was not improved using **1a**. The yield of **2q** was considerably improved to 72% using spacer-modified polymer **1d** (Table 4, entry 2).

Then, the aldol reaction of more hindered aryl ester, 2,6-di-*tert*-butyl-4-methylphenyl propionate (BHT propionate) with aldehydes was examined to improve *syn*/*anti* ratio of the product. The reaction of BHT propionate and benzaldehyde using polymer **1a** afforded aldol **2r** with higher stereoselectivity (*syn*/*anti*=7:93) but in low yield (25%) (Table 4, entry 3). The yield was enhanced to 92% using spacer-modified polymer **1d** with high *anti*-selectivity (Table 4, entry 4). Then, the aldol reaction of BHT propionate with cyclohexanecarbaldehyde, 2-methylpropanal, and butanal was examined using polymer **1d** and the corresponding *anti*-aldols **2s**–**u** were obtained in good to high yields with very high stereoselectivities (Table 4, entries 5–7).

2.7. Aldol reaction of *N*,*N*-dimethylpropionamide with aldehydes using polymer-bound lithium dialkylamides

The generation of enolate and its reaction was also examined for *N*,*N*-dimethylpropionamide. 3-Hydroxy-2,*N*,*N*-trimethyl-3-phenylpropionamide (**2v**) was obtained in 77% yield (*syn*/*anti*=64:36) by the reaction with

Table 5. Aldol reaction of *N*,*N*-dimethylpropionamide with aldehydes using polymer-bound lithium dialkylamides



Entry	R	Adduct	Base	Conditions[a]	Yield (%)[b]	*syn*:*anti*[c]
1	Ph	**2v**	**1a**	A	77	64:36
2	Ph	**2v**	**1a**	B	96	64:36
3	Ph	**2v**	**1d**	B	99 (97)[d]	62:38 (59:41)[d]
4	$Ph(CH_2)_2$	**2w**	**1a**	B	88	74:26
5	$Ph(CH_2)_2$	**2w**	**1d**	B	83	74:26
6	*c*-C_6H_{11}	**2x**	**1a**	B	93	86:14
7	*c*-C_6H_{11}	**2x**	**1d**	B	93	82:18
8	*i*-Pr	**2y**	**1a**	B	94	85:15
9	*i*-Pr	**2y**	**1d**	B	98	84:16

[a] Conditions A: the enolate was generated at −78 °C for 15 min. Conditions B: the enolate was generated at −78 °C for 15 min and then the resulting mixture was allowed to warm to rt for 15 min.
[b] Isolated yield of aldol **2v**–**y**.
[c] Determined by ^{1}H NMR analysis.
[d] The figures in parentheses are the results obtained by using LDA in place of polymer-bound lithium amides **1a** and **1d**.

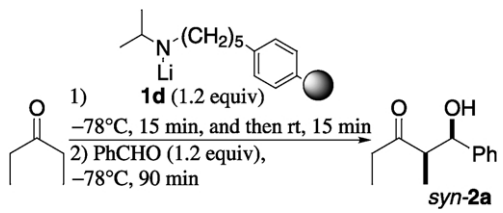
benzaldehyde after the generation of the enolate under Conditions A using **1a** (Table 5, entry 1). The yield was improved to 96% by employing Conditions B (Table 5, entry 2). Almost quantitative yield was achieved when **1d** was used in place of **1a** (Table 5, entry 3).

The reaction was applied to 3-phenylpropanal, cyclohexanecarbaldehyde, and 2-methylpropanal using **1a** and **1d** under Conditions B. Corresponding adducts **2w**–**y** were obtained in high yields with good *syn*/*anti* selectivities (Table 5, entries 4–9).

2.8. Reusability of polymer-bound lithium dialkylamide for the aldol reaction

As the usefulness of spacer-modified polymer-bound lithium dialkylamide **1d** was realized in the aldol reaction of ketones and carboxylic acid derivatives with aldehydes to afford various β-hydroxycarbonyl compounds, its recovery and repeated use were examined in the reaction between 3-pentanone and benzaldehyde under Conditions B. After quenching the aldol reaction using phosphate buffer (pH 7), the mixture was filtered through a glass filter. The recovered spacer-modified polymer-bound amine **3d** was successively rinsed with dichloromethane and water, and then dried under vacuum at 90 °C for 16 h. The dried polymer **3d** swollen in THF was then treated with a hexane solution of butyllithium to regenerate polymer-bound lithium dialkylamide **1d** by the same procedure for the conversion of a new precursor **3d** to polymer **1d**. The regenerated polymer **1d** was used in the aldol reaction between 3-pentanone and benzaldehyde again. The results are shown in Table 6. The yield and *syn*/*anti* selectivity of aldol adduct **2a** scarcely changed after the polymer-bound lithium dialkylamide **1d** was used five times.

Table 6. Reuse of polymer-bound lithium dialkylamide



Batch no.	Yield of **2a** (%)[a]	*syn*:*anti*[b]
1	90	73:37
2	87	70:30
3	89	69:31
4	90	70:30
5	89	71:29
6	89	69:31

[a] Isolated yield of aldol **2a**.
[b] Determined by ^{1}H NMR analysis.

3. Conclusions

Various polymer-bound lithium dialkylamides **1a**–**f** cross-linked with divinylbenzene were derived from the corresponding *N*-isopropyl-ω-(vinylphenyl)alkylamines (**4a**–**f**). The spacer served for an increase of the reactivity of the reagent, and **1b**–**f** was more effective than **1a** in crossed aldol reaction, although polymer **1a** promoted the reaction between *N*,*N*-dimethylpropionamide and aldehydes in good yields. In particular, **1d** modified with a pentamethylene spacer effectively promoted crossed aldol reaction between various carbonyl compounds and aldehydes to afford the corresponding adducts in up to 99% yield. The reagent showed higher *syn*/*anti* selectivities compared to those obtained using LDA under homogeneous conditions in most cases. The method for the recovery and reuse of the base **1d** was also demonstrated. The effect of the alkylene spacers on the reactivity of the polymer-bound lithium dialkylamide revealed by this work would be useful for the attachment of valuable lithium dialkylamides, e.g. chiral lithium dialkylamides, onto the polymer.

4. Experimental

4.1. General

All air-sensitive reactions were carried out under an atmosphere of argon. Tetrahydrofuran (THF) and diethyl ether were distilled under argon over sodium benzophenone ketyl before use. 4-Vinylbenzyl chloride was distilled over calcium hydride under reduced pressure. Lithium tetrachlorocuprate in tetrahydrofuran was purchased from Aldrich. Commercially available solution of butyllithium in hexane (Kanto Chemical Co., Inc.) was used to generate lithium dialkylamides. Proton NMR spectra were measured with a JEOL MY60 spectrometer at 60 MHz, a JEOL EX270 spectrometer at 270 MHz, or with a JEOL AL400 spectrometer at 400 MHz, using $CDCl_3$ as solvent. Carbon NMR spectra were recorded at 68 MHz with a JEOL EX270 spectrometer or at 100 MHz with a JEOL AL400 spectrometer using $CDCl_3$ as solvent. The chemical shifts are given in ppm relative to tetramethylsilane (δ scale) used as an internal standard. Infrared spectra were taken on a Perkin–Elmer Paragon 1000 spectrometer. Mass spectra were measured on a JEOL JMS-600 mass spectrometer using electron impact (EI). Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were carried out on a Perkin–Elmer 2400 CHN analyzer or a Perkin–Elmer 2400 II CHNS/O analyzer. TLC analyses were done on silica-gel 60 F_{254}-coated plates (E. Merck). Column chromatography was carried out with Wakogel C-200 gel unless otherwise specified. Preparative TLC was performed on silica-gel-coated plates (Wakogel B-5F, 20 cm×20 cm).

4.2. Preparation of 4-vinylbenzylmagnesium chloride

A solution of 4-vinylbenzyl chloride (25.0 g, 0.165 mol) in diethyl ether (25 mL) was added dropwise to a mixture of magnesium (4.5 g, 0.19 mol) for 2 h after activation of magnesium with a small piece of iodine in diethyl ether (75 mL) at 0 °C. After stirring for 1 h at 0 °C, the reaction temperature was allowed to increased to rt for 30 min and the mixture was stirred for 1 h. The resulting solution was directly used for the next cross-coupling reaction.

4.3. Synthesis of ω-bromoalkylstyrenes

4.3.1. 1-(4-Bromobutyl)-4-vinylbenzene (5c). A solution of 4-vinylbenzylmagnesium chloride prepared from

0.165 mol of 4-vinylbenzyl chloride in diethyl ether (100 mL) was added dropwise for 3 h to a solution of 1,3-dibromopropane (33.3 g, 0.165 mol) in THF (150 mL) in the presence of lithium tetrachlorocuprate (0.1 M, 15 mL, 1.5 mmol) at 0 °C.[33] After the addition was completed the mixture was stirred overnight at rt. Methanol (5 mL) was then added to cease the reaction. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure in the presence of 2,2-diphenyl-1-picrylhydrazil (DPPH). The resulting mixture was poured into water and extracted with toluene (3×50 mL). The combined organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. Then the residue was distilled in vacuo in the presence of DPPH to give 1-(4-bromobutyl)-4-vinylbenzene (20.9 g, 53%) as a colorless oil (bp 77 °C/0.028 mmHg). IR (neat): 3085, 3005, 2938, 2858, 1629, 1512, 1458, 1437, 1407, 1251, 991, 907, 844, 827; ^{1}H NMR ($CDCl_3$): 1.70–1.94 (m, 4H), 2.62 (t, J=7.3 Hz, 2H), 3.40 (t, J=6.6 Hz, 2H), 5.19 (dd, J=1.0, 10.9 Hz, 1H), 5.71 (dd, J=1.0, 17.8 Hz, 1H), 6.69 (dd, J=10.7, 17.7 Hz, 1H), 7.13 (d, J=7.9 Hz, 2H), 7.33 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): 29.7, 32.1, 33.6, 34.6, 113.0, 126.2, 128.5, 135.3, 136.5, 141.5; MS: m/z (%): 240 (M^++2, 23), 238 (M^+, 23), 117 (100), 115 (13), 91 (8). Exact mass for $C_{12}H_{15}Br$: 238.0357. Found 238.0357.

4.3.2. 1-(5-Bromopentyl)-4-vinylbenzene (5d). By a procedure similar to that for 1-(4-bromobutyl)-4-vinylbenzene (**5c**), the cross-coupling reaction with 1,4-dibromobutane (35.6 g, 0.165 mol) and 4-vinylbenzylmagnesium chloride was conducted to give 1-(5-bromopentyl)-4-vinylbenzene as a colorless oil (22.4 g, 54%). Bp 98 °C/0.045 mmHg; IR (neat): 3085, 2934, 2857, 1630, 1512, 1459, 1246, 991, 906, 832; ^{1}H NMR ($CDCl_3$): 1.41–1.54 (m, 2H), 1.58–1.69 (m, 2H), 1.83–1.93 (m, 2H), 2.61 (t, J=7.6 Hz, 2H), 3.40 (t, J=6.8 Hz, 2H), 5.20 (dd, J=0.99, 10.9 Hz, 1H), 5.70 (d, J=0.99, 17.5 Hz, 1H), 6.69 (dd, J=10.9, 12.8 Hz, 1H), 7.13 (d, J=7.9 Hz, 2H), 7.33 (d, J=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): 27.8, 30.5, 32.6, 33.8, 35.4, 112.9, 126.1, 128.5, 135.2, 136.6, 142.0; MS: (m/z) %: 254 (M^++2, 23), 252 (M^+, 11), 117 (100), 115 (12), 91 (8). Exact mass for $C_{13}H_{17}Br$: 252.0514. Found 252.0512.

4.3.3. 1-(6-Bromohexyl)-4-vinylbenzene (5e). By a procedure similar to that for 1-(4-bromobutyl)-4-vinylbenzene (**5c**), the cross-coupling reaction with 1,5-dibromopentane (37.9 g, 0.165 mol) and 4-vinylbenzylmagnesium chloride was conducted to give 1-(6-bromohexyl)-4-vinylbenzene as a colorless oil (15.8 g, 36%). Bp 104 °C/0.045 mmHg. IR (neat): 3085, 3006, 2933, 2857, 2361, 1630, 1512, 1458, 1438, 1259, 1225, 991, 907, 839; ^{1}H NMR ($CDCl_3$): 1.26–1.68 (m, 6H), 1.80–1.95 (m, 2H), 2.60 (t, J=7.6 Hz, 2H), 3.40 (t, J=6.9 Hz, 2H), 5.19 (dd, J=0.99, 10.9 Hz, 1H), 5.70 (dd, J=0.99, 17.8 Hz, 1H), 6.69 (dd, J=10.9, 17.8 Hz, 1H), 7.13 (d, J=7.9 Hz, 2H), 7.33 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): 28.0, 28.3, 31.2, 32.7, 34.0, 35.5, 112.7, 126.0, 128.4, 134.9, 136.5, 142.1; MS: (m/z) %: 268 (M^++2, 25), 266 (M^+, 28), 118 (15), 117 (100), 115 (11), 91 (8). Exact mass for $C_{14}H_{19}Br$: 266.0670. Found: 266.0670.

4.3.4. 1-(7-Bromoheptyl)-4-vinylbenzene (5f). By a similar to that procedure for 1-(4-bromobutyl)-4-vinylbenzene (**5c**), the cross-coupling reaction with 1,6-dibromohexane (40.3 g, 0.165 mol) and 4-vinylbenzylmagnesium chloride was conducted to yield 1-(7-bromoheptyl)-4-vinylbenzene as a colorless oil (18.0 g, 39%). Bp 114 °C/0.060 mmHg. IR (neat): 3085, 3005, 2934, 2858, 1907, 1817, 1629, 1512, 1458, 1437, 1251, 991, 907, 844; ^{1}H NMR ($CDCl_3$): 1.31–1.46 (m, 6H), 1.55–1.66 (m, 2H), 1.84 (quint, J=7.1 Hz, 2H), 2.59 (t, J=7.6 Hz, 2H), 3.39 (t, J=6.9 Hz, 2H), 5.18 (d, J=11.9 Hz, 1H), 5.69 (d, J=16.5 Hz, 1H), 6.68 (dd, J=10.9, 17.5 Hz, 1H), 7.12 (d, J=7.9 Hz, 2H), 7.32 (d, J=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): 28.1, 28.7, 29.1, 31.3, 32.8, 34.0, 35.6, 112.7, 126.0, 128.4, 134.9, 136.5, 142.3; MS: (m/z) %: 282 (M^++2, 26), 280 (M^+, 26), 118 (15), 117 (100), 115 (10), 91 (8). Exact mass for $C_{15}H_{21}Br$: 280.0827. Found 280.0829.

4.4. Synthesis of ω-(isopropylamino)alkylstyrenes (4a–f)

4.4.1. *N*-Isopropyl-4-vinylbenzylamine (4a). To isopropylamine (47.3 g, 0.40 mol) was added 4-vinylbenzyl chloride (30.5 g, 0.20 mol) at 0 °C and the mixture was stirred at rt for 24 h. Then dichloromethane and 4 M aqueous solution of sodium hydroxide were added to the reaction mixture. The aqueous solution was extracted with dichloromethane. The combined organic layer was washed with saturated aqueous sodium chloride solution and was dried with anhydrous sodium carbonate. The solvent and isopropylamine were evaporated and the residual oil was purified by column chromatography (silica gel, hexane/ethyl acetate=10:1) and distillation under reduced pressure in the presence of 2,2-diphenyl-1-picrylhydrazil (DPPH) to yield *N*-isopropyl-4-vinylbenzylamine[36,37] as a colorless oil (28.0 g, 80%), bp 66 °C/0.6 mmHg (lit.[36] bp 68 °C/1 mmHg). IR (neat): 3307, 2966, 1630, 1511, 1470, 1380, 1338, 1175, 990, 906, 830, 757, 721; ^{1}H NMR ($CDCl_3$): 1.08 (d, J=6.3 Hz, 6H), 1.36 (br s, 1H), 2.83 (sept, J=6.2 Hz, 1H), 3.75 (s, 2H), 5.20 (dd, J=0.66, 10.9 Hz, 1H), 5.71 (dd, J=1.0, 17.5 Hz, 1H), 6.69 (dd, J=10.9, 17.5 Hz, 1H), 7.27 (d, J=8.2 Hz, 2H), 7.37 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): 22.8, 47.9, 51.2, 113.2, 126.1, 128.2, 136.1, 136.5, 140.3.

4.4.2. *N*-Isopropyl-2-(vinylphenyl)ethylamine (4b). To 15.4 g of distilled technical 55 wt% divinylbenzene (65 mmol) in THF (48 mL) was added dropwise the mixture of isopropylamine (3.84 g, 65 mmol) in THF (17 mL) and a hexane solution of butyllithium (1.57 M solution, 1.7 mL, 2.6 mmol) for 2 h at 0 °C.[32] After stirring for 36 h at 0 °C, 2-propanol was added to the reaction mixture. The resulting mixture was concentrated under reduced pressure, diluted with ethyl acetate, and washed with water. The organic layer was dried over sodium sulfate and concentrated. The residue was distilled in vacuo in the presence of 2,2-diphenyl-1-picrylhydrazil (DPPH) to give *N*-isopropyl-2-(vinylphenyl)-ethylamine as a colorless oil (6.38 g, 52%), bp 49 °C/0.030 mmHg. IR (neat): 3306, 3087, 3007, 2965, 2867, 2827, 1630, 1512, 1474, 1442, 1379, 1338, 1174, 990, 906, 714; ^{1}H NMR ($CDCl_3$): 1.02 (d, J=6.1 Hz, 6H), 2.38–3.00 (m, 5H), 5.12 (d, J=10.8 Hz, 1H), 5.72 (d, J=17.4 Hz, 1H), 6.64 (dd, J=10.1, 17.5 Hz, 1H), 6.94–7.38 (m, 4H); MS: (m/z) %: 189 (M^+, 2), 131 (15), 117 (10), 115 (12), 91 (13), 72 (100). Exact mass for $C_{13}H_{19}N$: 189.1518. Found 189.1517.

4.4.3. *N*-Isopropyl-4-(4-vinylphenyl)butylamine (4c). To 1-(4-bromobutyl)-4-vinylbenzene (4.78 g, 20 mmol) was added isopropylamine (4.73 g, 80 mmol) at 0 °C. After stirring at room temperature for 48 h, 4 M aqueous solution of sodium hydroxide was added to the reaction mixture until most precipitate dissolved. The aqueous solution was extracted with dichloromethane. The combined organic layer was washed with saturated aqueous sodium chloride solution and was dried with anhydrous sodium carbonate. The solvent and isopropylamine were evaporated, and the residual oil was purified by silica gel chromatography with Chromatorex DM1020 (−100+200 mesh, Fuji Silysia Chemical Ltd) using hexane/ether (1:0–0:1) as eluent, giving *N*-isopropyl-4-(4-vinylphenyl)butylamine as a colorless oil (3.72 g, 86%). IR (neat): 3086, 2932, 2864, 1630, 1512, 1472, 1379, 1174, 990, 904, 842; ^{1}H NMR ($CDCl_3$): 1.04 (d, *J*=6.3 Hz, 6H), 1.48–1.68 (m, 4H), 2.57–2.64 (m, 4H), 2.76 (sept, *J*=6.3 Hz, 1H), 5.18 (dd, *J*=0.66, 10.9 Hz, 1H), 5.70 (dd, *J*=0.50, 17.3 Hz, 1H), 6.20 (dd, *J*=10.9, 17.8 Hz, 1H), 7.13 (d, *J*=8.6 Hz, 2H), 7.31 (d, *J*=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): 23.0, 29.3, 30.1, 35.6, 47.4, 48.7, 112.8, 126.1, 128.6, 135.1, 136.7, 142.3; MS: (*m*/*z*) %: 217 (M^+, 40), 202 (57), 117 (34), 72 (100). Exact mass for $C_{15}H_{23}N$: 217.1831. Found 217.1830.

4.4.4. *N*-Isopropyl-5-(4-vinylphenyl)pentylamine (4d). By a procedure similar to that for *N*-isopropyl-4-(4-vinylphenyl)butylamine, alkylation of isopropylamine (4.73 g, 80 mmol) with 1-(5-bromopentyl)-4-vinylbenzene (5.06 g, 20 mmol) was conducted to yield *N*-isopropyl-5-(4-vinylphenyl)pentylamine as a colorless oil (4.07 g, 83%). IR (neat): 3291, 3085, 2964, 2930, 2856, 1630, 1562, 1512, 1461, 1378, 1362, 1174, 990, 905, 842; ^{1}H NMR ($CDCl_3$): 1.04 (d, *J*=6.3 Hz, 6H), 1.26–1.41 (m, 2H), 1.45–1.54 (m, 2H), 1.56–1.68 (m, 2H), 2.57 (t, *J*=7.3 Hz, 2H), 2.60 (t, *J*=7.6 Hz, 2H), 2.77 (sept, *J*=6.3 Hz, 1H), 5.18 (dd, *J*=0.99, 10.9 Hz, 1H,), 5.70 (dd, *J*=0.99, 17.5 Hz, 1H), 6.69 (dd, *J*=10.9, 17.8 Hz, 1H), 7.13 (d, *J*=7.9 Hz, 2H), 7.33 (d, *J*=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): 22.9, 27.0, 30.2, 31.2, 35.5, 47.4, 48.6, 112.7, 126.0, 128.4, 135.0, 136.6, 142.3; MS: (*m*/*z*) %: 231 (M^+, 32), 217 (10), 216 (60), 117 (29), 72 (100). Exact mass for $C_{16}H_{25}N$: 231.1987. Found 231.1986.

4.4.5. *N*-Isopropyl-6-(4-vinylphenyl)hexylamine (4e). By a procedure similar to that for *N*-isopropyl-4-(4-vinylphenyl)butylamine, alkylation of isopropylamine (4.73 g, 80 mmol) with 1-(6-bromohexyl)-4-vinylbenzene (5.34 g, 20 mmol) was conducted to yield *N*-isopropyl-6-(4-vinylphenyl)hexylamine as a colorless oil (3.58 g, 73%). IR (neat): 3350, 3085, 2963, 2855, 1630, 1512, 1465, 1406, 1378, 1337, 1262, 1174, 1120, 991, 904, 831; ^{1}H NMR ($CDCl_3$): 1.04 (d, *J*=5.9 Hz, 6H), 1.32–1.64 (m, 8H), 2.54–2.74 (m, 4H), 2.77 (sept, *J*=6.3 Hz, 1H), 5.18 (d, *J*=9.9 Hz, 1H), 5.69 (d, *J*=17.8 Hz, 1H), 6.69 (dd, *J*=10.9, 17.5 Hz, 1H), 7.12 (d, *J*=7.9 Hz, 2H), 7.32 (d, *J*=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): 21.6, 27.1, 28.8, 29.0, 31.2, 35.5, 46.5, 49.2, 112.8, 126.1, 128.5, 135.0, 136.6, 142.4; MS: (*m*/*z*) %: 245 (M^+, 28), 231 (11), 230 (58), 128 (16), 117 (28), 72 (100). Exact mass for $C_{17}H_{27}N$: 245.2144. Found 245.2144.

4.4.6. *N*-Isopropyl-7-(4-vinylphenyl)heptylamine (4f). By a procedure similar to that for *N*-isopropyl-4-(4-vinylphenyl)butylamine, alkylation of isopropylamine (4.73 g, 80 mmol) with 1-(7-bromoheptyl)-4-vinylbenzene (5.62 g, 20 mmol) was conducted to yield *N*-isopropyl-7-(4-vinylphenyl)heptylamine as a colorless oil (4.03 g, 78%). IR (neat): 3086, 2932, 2864, 1630, 1512, 1472, 1379, 1174; ^{1}H NMR ($CDCl_3$): 1.04 (d, *J*=6.3 Hz, 6H), 1.25–1.41 (m, 6H), 1.32 (br s, 1H), 1.43–1.51 (m, 2H), 1.54–1.65 (m, 2H), 2.50–2.61 (m, 4H), 2.77 (sept, *J*=6.3 Hz, 1H), 5.18 (dd, *J*=1.0, 10.9 Hz, 1H,), 5.69 (dd, *J*=1.0, 17.5 Hz, 1H), 6.69 (dd, *J*=10.9, 17.5 Hz, 1H), 7.13 (d, *J*=7.9 Hz, 2H), 7.32 (d, *J*=7.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): 23.1, 27.4, 29.2, 29.4, 30.5, 31.4, 35.7, 47.6, 48.7, 112.6, 125.9, 128.4, 134.9, 136.6, 142.4; MS: (*m*/*z*) %: 259 (M^+, 46), 245 (25), 244 (100), 117 (27), 115 (10). Exact mass for $C_{18}H_{29}N$: 259.2300. Found 259.2302.

4.5. Preparation of polymer-bound *N*-isopropyl-ω-(vinylphenyl)alkylamine (3a–f)

Preparation of 2 mol% cross-linked, 20 mol% ring-substituted ω-isopropylaminoalkylated polystyrene in microporous form was carried out by the suspension copolymerization of *N*-isopropyl-ω-(vinylphenyl)alkylamine (20 mol%), styrene (78 mol%), and divinylbenzene (2 mol%) by the procedure described.[30,38] Polymer-bound *N*-isopropyl-4-vinylbenzylamine (**3a**) was prepared according to the literature procedure.[30]

4.5.1. Polymer-bound *N*-isopropyl-5-(4-vinylphenyl)-pentylamine (3d). A solution of gelatin (0.106 g), poly(diallyldimethylammonium chloride-*co*-sulfur dioxide) (1.1 g, from Nittobo, Japan), boric acid (0.41 g, 5.9 mmol), and sodium nitrate (23 mg, 0.33 mmol) in water (33 mL) was adjusted to pH 9.5 with 25 wt% aqueous sodium hydroxide and was placed in a 50 mL round-bottom flask fitted with a reflux condenser and a mechanical stirrer. To the solution was added a mixture of *N*-isopropyl-5-(4-vinylphenyl)pentylamine (1.39 g, 6.0 mmol), styrene (2.44 g, 23.4 mmol), 142 mg of technical 55% divinylbenzene (0.60 mmol), and 2,2′-azobisisobutyronitrile (32 mg, 0.19 mmol). The flask was purged with nitrogen for 40 min at rt, and a nitrogen atmosphere was maintained throughout the polymerization. The mixture was stirred at 70 °C for 1 day. Stirring speed in this preparation was 430 rpm. The insoluble polymer was obtained by filtration with a glass funnel, and it was washed thoroughly with hot water, methanol, THF, and CH_2Cl_2, successively. Cross-linked polymer-bound reagent **3d** was obtained as beads after removal of the solvent under reduced pressure (<1 mmHg) at 90 °C for 16 h. Sieving the polymer beads through a sieve (50–100 mesh) gave the fraction (2.97 g, 76%) of uniform particle size. The amine content determined by elemental analysis (C, 88.51; H, 9.05; N, 2.35) was 1.68 mmol/g. IR (KBr): 3083, 3060, 2925, 1493, 1377, 836, 758, 699.

4.5.2. Polymer-bound *N*-isopropyl-2-(vinylphenyl)ethylamine (3b). The title compound was obtained by a procedure similar to that for polymer-bound *N*-isopropyl-5-(4-vinylphenyl)pentylamine (83% yield). The amine content determined by elemental analysis (C, 88.41; H, 9.06; N, 2.30) was 1.64 mmol/g. IR (KBr): 3433, 3026,

2962, 2924, 2850, 1602, 1493, 1451, 1377, 1174, 1028, 758, 699, 540.

4.5.3. Polymer-bound *N*-isopropyl-4-(4-vinylphenyl)-butylamine (3c). The title compound was obtained by a procedure similar to that for polymer-bound *N*-isopropyl-5-(4-vinylphenyl)pentylamine (82% yield). The amine content determined by elemental analysis (C, 88.97; H, 10.54; N, 2.38) was 1.70 mmol/g. IR (KBr): 3433, 3026, 2962, 2924, 2850, 1602, 1493, 1451, 1377, 1174, 1028.

4.5.4. Polymer-bound *N*-isopropyl-6-(4-vinylphenyl)-hexylamine (3e). The title compound was obtained by a procedure similar to that for polymer-bound *N*-isopropyl-5-(4-vinylphenyl)pentylamine (73% yield). The amine content determined by elemental analysis (C, 86.99; H, 10.41; N, 2.23) was 1.59 mmol/g. IR (KBr): 3313, 3083, 3060, 3027, 2922, 2853, 1666, 1602, 1511, 1492, 1452, 1378, 1362, 1336, 1173, 1029.

4.5.5. Polymer-bound *N*-isopropyl-7-(4-vinylphenyl)-heptylamine (3f). The title compound was obtained by a procedure similar to that for polymer-bound *N*-isopropyl-5-(4-vinylphenyl)pentylamine (67% yield). The amine content determined by elemental analysis (C, 87.99; H, 9.88; N, 2.05) was 1.46 mmol/g. IR (KBr): 3315, 3083, 3061, 3027, 2925, 2853, 1660, 1602, 1511, 1494, 1453, 1378, 1337, 1179, 1029.

4.6. Aldol reactions using polymer-bound lithium dialkylamides (1a–f), general procedure

Conditions A. To a suspension of polymer-bound *N*-isopropyl-4-vinylbenzylamine **3a** (amine content: 1.68 mmol/g; particle size: 50–100 mesh; cross-linked with 2 mol% of divinylbenzene, 750 mg, 1.3 mmol) in THF (6 mL) was added a hexane solution of butyllithium (1.54 M, 0.78 mL, 1.2 mmol) at rt and the reaction mixture was stirred for 0.5 h. Carbonyl compound (1.0 mmol) in THF (2 mL) was added dropwise to the reaction mixture at −78 °C and stirring was continued for 15 min. A THF (2 mL) solution of aldehyde (1.2 mmol) was added to the mixture at −78 °C. After keeping the temperature at −78 °C for 90 min, the reaction was quenched with phosphate buffer (pH 7). The resin was filtered off, washed with CH_2Cl_2 and H_2O, and dried in vacuo at 90 °C for 16 h. The organic filtrate was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by preparative TLC or silica-gel chromatography, giving the β-hydroxycarbonyl compound.

Conditions B. To a suspension of polymer-bound *N*-isopropyl-4-vinylbenzylamine **3a** (amine content: 1.68 mmol/g; particle size: 50–100 mesh; cross-linked with 2 mol% of divinylbenzene, 750 mg, 1.3 mmol) in THF (6 mL) was added a hexane solution of butyllithium (1.54 M, 0.78 mL, 1.2 mmol) at rt and the reaction mixture was stirred for 0.5 h. Carbonyl compound (1.0 mmol) in THF (2 mL) was added dropwise to the reaction mixture at −78 °C and stirring was continued for 15 min. The mixture was allowed to warm at rt for 15 min and was cooled to −78 °C again. Then a THF (2 mL) solution of aldehyde (1.2 mmol) was added to the mixture. After keeping the temperature at −78 °C for 90 min, the reaction was quenched with phosphate buffer (pH 7). The resin was filtered off, washed with CH_2Cl_2 and H_2O, and dried in vacuo at 90 °C for 16 h. The organic filtrate was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by preparative TLC or silica-gel chromatography, giving the β-hydroxycarbonyl compound.

4.6.1. 1-Hydroxy-2-methyl-1-phenyl-3-pentanone (2a). Yield 90% as a colorless oil (Table 1, entry 8); data consistent with that reported in literatures.[39,40]

4.6.2. 1-(4-Chlorophenyl)-1-hydroxy-2-methyl-3-pentanone (2b). Yield 88% as a colorless oil (Table 2, entry 2); data consistent with that reported in a literature.[39]

4.6.3. 1-Hydroxy-1-(2-methoxyphenyl)-2-methyl-3-pentanone (2c). Yield 84% as a colorless oil (Table 2, entry 3). Aldol **2c** was further purified by preparative thin-layer chromatography (silica-gel, hexane/diethyl ether 3:1) to separate *syn*-**2c** and *anti*-**2c** as colorless oils; data consistent with that reported in a literature.[39]

4.6.4. 5-Hydroxy-4-methyl-7-phenyl-6-hepten-3-one (2d). Yield 93% as a pale yellow oil (Table 2, entry 4); data consistent with that reported in a literature.[39]

4.6.5. 1-Cyclohexyl-1-hydroxy-2-methyl-3-pentanone (2e). Yield 82% as a colorless oil (Table 2, entry 5); data consistent with that reported in literatures.[41,42]

4.6.6. 5-Hydroxy-4-methyl-7-phenyl-3-heptanone (2f). Yield 88% as a colorless oil (Table 2, entry 6); data consistent with that reported in literatures.[39,40]

4.6.7. 5-Hydroxy-4-methyl-3-octanone (2g). Yield 65% as a colorless oil (Table 2, entry 7); data consistent with that reported in literatures.[41,42]

4.6.8. 2-(Hydroxyphenylmethyl)cyclohexanone (2h). Yield 82% as a white solid (Table 2, entry 8). Aldol **2h** was further purified by preparative thin-layer chromatography (silica-gel, hexane/diethyl ether 3:1) to separate *syn*-**2h** and *anti*-**2h** as white crystals; data consistent with that reported in literatures.[43,44]

4.6.9. 2-(1-Hydroxy-2-methylpropyl)cyclohexanone (2i). Yield 59% as a colorless oil (Table 2, entry 9); data consistent with that reported in literatures.[44–46]

4.6.10. 2-(1-Hydroxy-3-phenylpropyl)cyclohexanone (2j). Yield 56% as a viscous oil (Table 2, entry 10); data consistent with that reported in literatures.[47,48]

4.6.11. 1-Hydroxy-1-phenyl-3-hexanone (2k). Yield 88% as a colorless oil (Table 3, entry 3); data consistent with that reported in a literature.[49]

4.6.12. 6-Hydroxy-8-phenyl-4-octanone (2l). Yield 93% as a colorless oil (Table 3, entry 5); IR (neat): 3464, 3027, 2934, 2875, 1708, 1496, 1455, 1408, 1378, 1128, 1098, 1032, 749, 701; ^{1}H NMR ($CDCl_3$): 0.91 (t, J=7.4 Hz, 3H),

1.53–1.89 (m, 4H), 2.39 (t, *J*=7.4 Hz, 2H), 2.47–2.87 (m, 2H), 2.57 (t, *J*=6.1 Hz, 2H), 3.49 (s, 1H), 4.00–4.10 (m, 1H), 7.18–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$): 13.5, 16.8, 31.6, 38.0, 45.3, 48.9, 66.7, 125.6, 128.2, 128.3, 141.7, 212.0; MS: (*m*/*z*) %: 220 (M^+, 8), 203 (13), 202 (72), 159 (15), 149 (22), 131 (24), 117 (23), 115 (15), 105 (11), 104 (11), 92 (23), 91 (86), 72 (14), 71 (100), 57 (16), 55 (11). Exact mass for $C_{14}H_{20}O_2$: 220.1463. Found 220.1465.

4.6.13. 1-Cyclohexyl-1-hydroxy-3-hexanone (2m). Yield 82% as a white solid (Table 3, entry 7); mp 39.2–40.4 °C; IR (neat): 3364, 3289, 2956, 2934, 2894, 2854, 1705, 1447, 1405, 1377, 1353, 1310, 1270, 1127, 1033, 993, 892, 883; ^{1}H NMR ($CDCl_3$): 0.90–1.41 (m, 9H), 1.55–1.87 (m, 7H), 2.42 (t, *J*=7.3 Hz, 2H), 2.48–2.64 (m, 2H), 2.97 (d, *J*=3.6 Hz, 1H), 3.55–3.77 (1H, m); ^{13}C NMR ($CDCl_3$): 13.4, 16.8, 25.9, 26.0, 26.2, 28.0, 28.6, 42.9, 45.4, 46.0, 71.5, 212.4. Exact mass for $C_{12}H_{22}O_2$: 198.1620. Found 198.1593.

4.6.14. 6-Hydroxy-7-methyl-4-octanone (2n). Yield 79% as a colorless oil (Table 3, entry 9); data consistent with that reported in a literature.[50]

4.6.15. 1-Hydroxy-5-methyl-1-phenyl-4-hexen-3-one (2o). Yield 81% as a colorless oil (Table 3, entry 11); IR (neat): 3448, 3086, 3062, 3030, 2975, 2910, 1681, 1618, 1494, 1449, 1383, 1359, 1204, 1115, 1063, 1043, 1013, 824, 800, 701; ^{1}H NMR ($CDCl_3$): 1.91 (d, *J*=1.3 Hz, 3H), 2.18 (d, *J*=1.3 Hz, 3H), 2.82 (s, 1H), 2.84 (d, *J*=0.66 Hz, 1H), 3.71 (d, *J*=2.4 Hz, 1H), 5.15–5.20 (m, 1H), 6.05 (s, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): 21.0, 27.8, 52.1, 70.1, 123.6, 125.6, 127.4, 128.4, 143.0, 157.6, 200.6; MS: (*m*/*z*) %: 204 (M^+, 16), 186 (14), 162 (18), 120 (35), 107 (15), 106 (13), 105 (38), 83 (100), 79 (16), 77 (28), 55 (22). Exact mass for $C_{13}H_{16}O_2$: 204.1150. Found 204.1153.

4.6.16. 4-Hydroxy-4-phenyl-2-butanone (2p). Yield 80% as a colorless oil (Table 3, entry 14); data consistent with that reported in a literature.[51]

4.6.17. 3-Hydroxy-2-methyl-3-phenylpropionic acid 2,6-dimetylphenyl ester (2q). Yield 72% as a highly viscous colorless oil (Table 4, entry 2); data consistent with that reported in literatures.[52,53]

4.6.18. 3-Hydroxy-2-methyl-3-phenylpropionic acid 2,6-di-*tert*-butyl-4-methylphenyl ester (2r). The *syn*/*anti* ratio was determined by ^{1}H NMR analysis of the crude product in comparison with the ^{1}H NMR data of the 3-hydroxy-2-methyl-3-phenylpropionic acid 2,6-dimethylphenyl ester.[52] Yield 92% as a highly viscous oil (Table 4, entry 4); data consistent with that reported in a literature.[53]

4.6.19. (2*R,3*R**)-3-Cyclohexyl-3-hydroxy-2-methyl-propionic acid 2,6-di-*tert*-butyl-4-methylphenyl ester (2s).** Yield 64% as a highly viscous oil (Table 4, entry 5); IR ($CHCl_3$): 3547, 2930, 2856, 1728, 1599, 1421, 1366, 1128, 1106; ^{1}H NMR ($CDCl_3$): 1.19–1.82 (m, 32H), 2.31 (s, 3H), 2.91 (quint, *J*=7.6 Hz, 1H), 3.53 (d, *J*=4.6 Hz, 1H), 3.59 (dt, *J*=3.7, 7.5 Hz, 1H), 7.12 (d, *J*=3.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): 13.6, 21.6, 25.3, 26.3, 26.5, 26.7, 30.6, 31.48, 31.52, 35.2, 35.3, 39.6, 43.2, 77.8, 126.9, 127.1, 134.7, 141.6, 141.9, 145.7, 176.9; Exact mass for $C_{25}H_{41}O_3$ $(M+H)^+$: 389.3058. Found 389.3056.

4.6.20. (2*R,3*R**)-3-Hydroxy-2,4-dimethylpentanoic acid 2,6-di-*tert*-butyl-4-methylphenyl ester (2t).** Yield 79% as a white solid (Table 4, entry 6); data consistent with that reported in a literature.[53]

4.6.21. 3-Hydroxy-2-methylhexanoic acid 2,6-di-*tert*-butyl-4-methylphenyl ester (2u). Yield 82% as a white solid (Table 4, entry 7); mp 93.5–94.4 °C; IR ($CHCl_3$): 3537, 2965, 2874, 1730, 1482, 1421, 1180, 1103; ^{1}H NMR ($CDCl_3$): 0.95 (t, *J*=7.0 Hz, 3H), 1.19–1.62 (m, 25H), 2.31 (s, 3H), 2.78 (quint, *J*=7.4 Hz, 1H), 3.49 (d, *J*=4.4 Hz, 1H), 3.81–3.89 (m, 0.97H), 4.15–4.19 (m, 0.03H), 7.12 (d, *J*=2.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): 13.5, 14.2, 18.6, 21.6, 31.45, 31.52, 35.2, 35.3, 36.1, 46.3, 72.4, 126.9, 127.1, 134.7, 141.6, 141.9, 145.7, 176.3; Exact mass for $C_{22}H_{37}O_3$ $(M+H)^+$: 349.2743. Found 349.2744.

4.6.22. 3-Hydroxy-2,*N*,*N*-trimethyl-3-phenylpropionamide (2v). Yield 99% as a white solid (Table 5, entry 3); data consistent with that reported in a literature.[54]

4.6.23. 3-Hydroxy-2,*N*,*N*-trimethyl-5-phenylpentanamide (2w). Yield 83% as a colorless oil (Table 5, entry 5); IR (neat): 3416, 2936, 1622, 1496, 1456, 1401, 1147, 1041, 930; ^{1}H NMR ($CDCl_3$): 1.10–1.26 (m, 3H), 1.49–1.99 (m, 2H), 2.55–2.72 (m, 2H), 2.85–3.02 (m, 7H), 3.59–3.65 (m, 0.26H), 3.91 (br d, *J*=9.2 Hz, 0.74H), 4.20–4.41 (m, 0.26H), 4.73 (br s, 0.74H), 7.15–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$): 9.7, 15.2, 32.3, 32.4, 35.3, 35.7, 37.3, 37.7, 40.0, 40.2, 70.3, 73.6, 125.6, 128.1, 128.4, 141.9, 142.1, 176.4, 177.5; MS: (*m*/*z*) %: 235 (M^+, 46), 217 (38), 149 (30), 144 (21), 130 (57), 111 (21), 101 (73), 91 (100), 83 (28), 72 (86), 69 (27), 57 (47), 55 (40). Exact mass for $C_{14}H_{21}NO_2$: 235.1572. Found 235.1570.

4.6.24. 3-Cyclohexyl-3-hydroxy-2,*N*,*N*-trimethyl-propionamide (2x). Yield 93% as a colorless oil (Table 5, entry 7); IR (neat): 3418, 2925, 2852, 1623, 1451, 1418, 1401, 1318, 1259, 1160, 1136, 983, 628; ^{1}H NMR ($CDCl_3$): 0.84–1.26 (m, 7H), 1.35–1.44 (m, 1H), 1.60–1.78 (m, 5H), 1.96–2.04 (m, 0.2H), 2.10–2.21 (m, 0.8H), 2.81–3.11 (m, 7H), 3.15–3.34 (m, 0.18H), 3.42–3.52 (m, 0.82H), 4.28 (d, *J*=8.6 Hz, 0.18H), 4.78 (s, 0.82H); ^{13}C NMR ($CDCl_3$): 9.5, 15.6, 26.1, 26.4, 26.5, 28.5, 28.7, 28.8, 29.9, 30.1, 35.3, 36.1, 37.4, 37.8, 39.5, 42.0, 75.4, 79.1, 177.0, 177.8; MS: (*m*/*z*) %: 214 (M^++1, 8), 213 (M^+, 4), 198 (46), 195 (40), 131 (10), 130 (100), 101 (96), 95 (14), 83 (10), 72 (57), 55 (11). Exact mass for $C_{12}H_{23}NO_2$: 213.1729. Found 213.1726.

4.6.25. 3-Hydroxy-2,4,*N*,*N*-tetramethylpentanamide (2y). Yield 98% as a colorless oil (Table 5, entry 9); IR (neat): 3423, 2961, 2875, 1625, 1508, 1467, 1419, 1401, 1260, 1163, 1103, 1002, 986; ^{1}H NMR ($CDCl_3$): 0.85 (d, *J*=7.3 Hz, 2.5H), 0.90 (d, *J*=6.6 Hz, 0.48H), 0.98 (d, *J*=6.6 Hz, 0.48H), 1.04 (d, *J*=6.6 Hz, 2.5H), 1.13 (d, *J*=7.3 Hz, 2.5H), 1.25 (d, *J*=7.3 Hz, 0.48H), 1.63–1.81 (m, 1H), 2.82–3.10 (m, 7H), 3.20–3.33 (m, 0.16H), 3.41 (d, *J*=9.2 Hz, 0.84H), 4.28 (d, *J*=7.9 Hz, 0.16H), 4.78 (s, 0.84H); ^{13}C NMR ($CDCl_3$): 9.5, 15.6, 18.2, 18.9, 19.8, 19.9,

30.2, 32.2, 35.5, 35.8, 36.7, 37.4, 76.7, 177.7; MS: (*m*/*z*) %: 174 (M^++1), 173 (M^+), 158 (52), 155 (20), 140 (17), 130 (100), 101 (83), 100 (20), 73 (19), 72 (96), 57 (15). Exact mass for $C_9H_{19}NO_2$: 173.1416. Found 173.1418.

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